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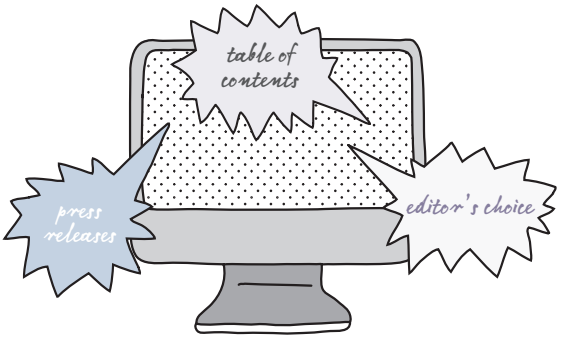

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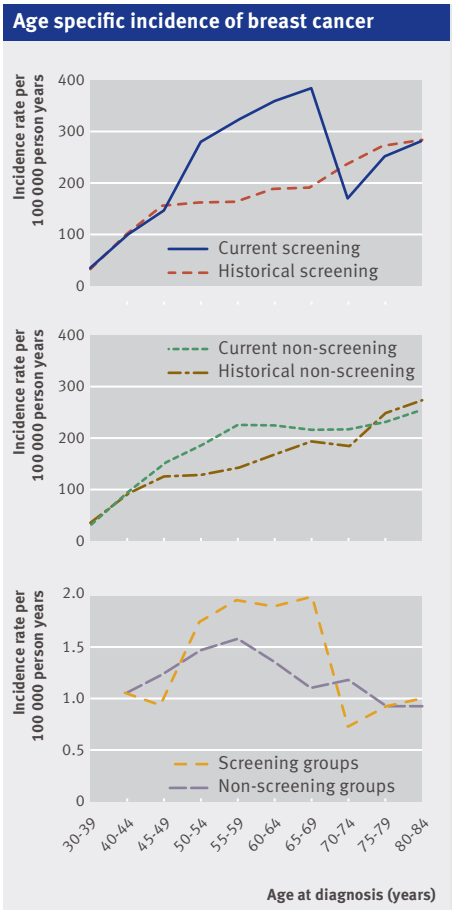
Screening overdiagnoses 6-10 women for every death from breast cancer prevented



Adapted from *Ann Intern Med* 2012;156:491-9

Researchers estimate that breast cancer would never have become apparent in 15-25% of women diagnosed through the Norwegian screening programme. For every 2500 women invited for screening, six to 10 women are overdiagnosed, 20 cases of breast cancer are detected and treated early, and one death from breast cancer is prevented.

Previous reports have estimated overdiagnosis in breast cancer screening programmes as between 0% and 54%. Rates of overdiagnosis are difficult to estimate because breast cancer trends irrespective of screening must be taken into account and lead time (the amount of time a diagnosis by mammography precedes a clinical diagnosis) must be adjusted for. The various methods used by researchers yield very different results, and there is no universally accepted method to estimate overdiagnosis.

The current researchers took advantage of a national screening programme that was gradually implemented by geographical region over nine years. Attendance was high. Only invasive breast cancer was taken into account and carcinoma in situ was excluded from the analysis. To account for temporal trends, the incidence of breast cancer with screening was compared with historical incidence in the same region before screening was implemented, as well as with concurrent incidence of breast cancer in counties not yet included in the screening programme. Two different methods were also used to adjust for lead time.

Since 2005, all Norwegian women aged 50-69 years have been invited for mammography every two years.

Ann Intern Med 2012;156:491-9

Fluoroquinolones may precipitate detachment of the retina

Four case reports have previously reported that fluoroquinolones might induce detachment of the retina. This has now been confirmed in a case-control study nested within a cohort of nearly one million patients who saw an ophthalmologist in British Columbia over a period of eight years.

Among 4384 patients with detachment of the retina, 145 were current users of fluoroquinolones, 12 took the drugs in the week before the diagnosis (recent users), and 288 took them during the previous year (former users). Each case was matched with 10 controls, for age and month of entry into the cohort. Analyses were adjusted for sex, history of cataract surgery, myopia, diabetes, number of visits to an ophthalmologist, and the number of prescription drugs taken in the previous year.

No excess risk of retinal detachment was seen for recent (0.3% of cases *v* 0.2% of controls; adjusted rate ratio 0.92, 95% CI 0.45 to 1.87) or past (6.6% *v* 6.1%; 1.03, 0.89 to 1.19) use of fluoroquinolones. However, the risk was increased 4.5-fold in current users (3.3% *v* 0.6%; 4.50, 3.56 to 5.70), with a number needed to harm of 2500. In the US, an estimated 1440 cases may be attributable to the use of fluoroquinolones each year.

It may be that fluoroquinolones damage collagen, which plays a major role in the integrity of the vitreous body. The damage may result in posterior vitreous detachment, thus increasing the risk of retinal detachment. In this study, ciprofloxacin was the most commonly prescribed fluoroquinolone (eight out of 10 patients). No increased risk of retinal detachment was seen among current users of β lactam antibiotics (0.74, 0.35 to 1.57) or short acting β agonists (0.95, 0.68 to 1.33).

JAMA 2012;307:1414-9

No support for MRI in early detection of breast cancer

The addition of ultrasound or magnetic resonance imaging (MRI) to mammography improves the detection of breast cancer but also increases false positive findings in women at increased risk.

More than 2700 women participated in a screening study in which both mammography and ultrasound were performed each year for a total of three years in a randomised order. All women had dense breast tissue on the first mammography screen and at least one other risk factor for breast cancer, most often a personal history of breast cancer. After three years, eligible women were offered free MRI, and 58% of these women accepted.

The addition of ultrasound to mammography helped identify an average of 4.3 extra cancers per 1000 women per year. The further addition of MRI detected an extra 14.7 cancers per 1000 women. To detect one case of breast cancer, 127 mammographies, 234 supplemental ultrasounds, and 68 supplemental MRIs needed to be performed.

However, of the 5% of screened women who had a biopsy just because of a positive ultrasound result, only 7.4% had cancer confirmed by histology or future clinical outcomes. Similarly, of the 126 women thought to have cancer just because of a positive MRI result, cancer was confirmed in only nine women. The researchers advise against adding MRI to mammography for breast cancer screening, given the high false positive rates, high cost, and low uptake among women offered MRI.

JAMA 2012;307:1394-404

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Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial

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STUDY QUESTION

Is cognitive therapy effective in preventing the worsening of emerging psychotic symptoms experienced by help seeking young people deemed to be at risk for serious conditions such as schizophrenia?

SUMMARY ANSWER

Cognitive therapy did not significantly reduce transition to psychosis or symptom related distress but did reduce the severity of psychotic symptoms in people at high risk.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

It seems possible to identify a population at high risk of developing psychosis, and several trials suggest promising interventions for prevention of psychosis and improvement in psychotic symptoms in these populations. The rates of transition were lower than previously thought and the potential for recovery with minimal intervention was high in this population. Cognitive therapy did not prevent transition to psychosis but did reduce the severity of psychotic symptoms.

Design

Randomised single blind controlled trial with block randomisation and computer generated allocation comparing cognitive therapy plus monitoring of mental state with monitoring of mental state only.

Participants and setting

Across five UK sites, 288 young people at high risk of psychosis (aged 14-35 years) were recruited. One hundred and forty four were assigned to cognitive therapy and 144 to monitoring of mental state alone.

Primary outcomes

Ratings on the comprehensive assessment of at risk mental states (CAARMS), which provides a dichotomous score for transition to psychosis and ordinal scores for severity of psychotic symptoms and distress.

Main results and the role of chance

Transition to psychosis based on intention to treat was analysed using discrete time survival models. Overall, the prevalence of transition was lower than expected (23/288, 8%), with no statistically significant difference between the two groups (proportional odds ratio 0.73, 95% confidence interval 0.32 to 1.68). Changes in severity of and distress from symptoms, as well as secondary outcomes, were analysed using random effects regression (analysis of covariance) adjusted for site and baseline symptoms. Distress from psychotic symptoms did not differ between the groups (estimated difference at 12 months −3.00, 95% confidence interval −6.95 to 0.94) but their severity was significantly reduced in the cognitive therapy group, with an estimated between group effect size at 12 months of −3.67 (−6.71 to −0.64, P=0.018).

Harms

No harms were identified, with both groups improving over time.

Bias, confounding, and other reasons for caution

Sixty seven blind breaks were reported, representing 22.2% of participants; therefore the blinding was successfully maintained in 77.8% of participants. Fifteen of these blind breaks were in the monitoring alone condition and 52 in the cognitive therapy condition. In cases where blinding was broken, another rater assessed the patient for all subsequent assessments, or the ratings were discussed with a blind rater and consensus reached (if there was a clinical justification not to switch). A significant proportion of data were missing, which could introduce bias; however, the proportions were similar for both groups.

Generalisability to other populations

Our observations suggest a review is required of the "ultra high risk" strategy, in particular the influence of community ascertainment strategies on risk and protective factors for psychosis and of natural recovery processes in adolescence and early adulthood. It seems highly premature to introduce a diagnostic category into the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, on the basis of risk of psychosis, given the low transition rate and high potential for natural recovery.

Study funding/potential competing interests

This research was funded by the Medical Research Council (G0500264) and the Department of Health. We have no competing interests.

Trial registration number

Current Controlled Trials ISRCTN56283883.

Results for comprehensive assessment of at risk mental states (CAARMS) and number of transitions for each group. Values are means (standard deviations) unless stated otherwise

CAARMS variables	Cognitive therapy plus monitoring (n=144)	Monitoring only (n=144)
Severity at baseline	38.72 (16.84), n=143	38.15 (17.80), n=143
Distress at baseline	42.77 (20.51), n=130	42.45 (19.62), n=134
Severity at 12 months	14.88 (15.54), n=95	20.84 (17.75), n=93
Distress at 12 months	14.72 (16.87), n=92	19.49 (18.26), n=91
No of transitions at 12 months	7	10

Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study

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STUDY QUESTION

Will lowering the diagnostic threshold of plasma troponin concentration to the 99th centile substantially increase the diagnosis of myocardial infarction and improve the identification of those at risk of recurrent myocardial infarction and death?

SUMMARY ANSWER

Lowering the diagnostic threshold to the 99th centile increased the diagnosis of myocardial infarction by 47% and identified patients who were four to five times more likely to die or have a recurrent myocardial infarct than those below this threshold.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The universal definition recommends the 99th centile of plasma troponin concentration as the diagnostic threshold for myocardial infarction if the assay achieves a coefficient of variation of ≤10%. Most assays are unable to achieve this level of accuracy, and most centres apply much higher diagnostic thresholds. Our study shows that accepting greater assay imprecision to permit the lowering of the diagnostic threshold to the 99th centile will identify patients at high risk of recurrent events but increases the diagnosis of myocardial infarction by 47%.

Participants and setting

Patients admitted with suspected acute coronary syndrome to a tertiary cardiac centre in Scotland.

Design, size, and duration

Cohort study of 2092 consecutive patients stratified with a sensitive troponin I assay into three groups (<0.012, 0.012-0.049, and ≥0.050 µg/L) based on the 99th centile for plasma troponin (0.012 µg/L; coefficient of variation 20.8%) and the diagnostic threshold (0.050 µg/L; 7.2%) and followed up for a minimum of one year.

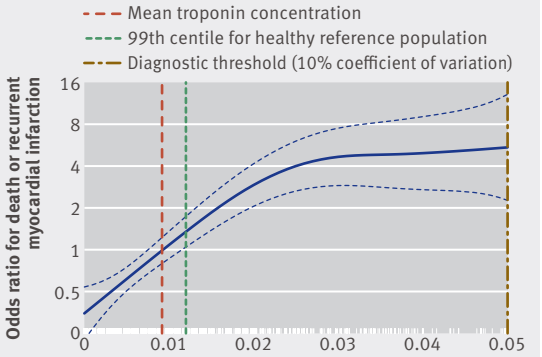
Primary outcome, risks, exposures

Event-free survival (recurrent myocardial infarction and death) at one year in patients grouped by plasma troponin concentrations.

Main results and the role of chance

Troponin I concentrations were <0.012 µg/L in 988 patients (47%), 0.012-0.049 µg/L in 352 patients (17%), and ≥0.050 µg/L in 752 patients (36%). Adoption of the 99th centile as the diagnostic threshold would increase the diagnosis of myocardial infarction from 752 to 1104: a relative increase of 47%. At one year, patients with troponin concentrations of 0.012-0.049 µg/L were more likely to be dead or to have been readmitted with recurrent myocardial infarction than those with troponin concentrations <0.012 µg/L (13% *v* 3%; odds ratio 4.8, 95% confidence interval 3.0 to 7.7; P<0.001). Compared with troponin ≥0.050 µg/L, patients with troponin 0.012-0.049 µg/L had a higher risk profile but were less likely to receive a diagnosis of, or be investigated and treated for, acute coronary syndrome.

Association between plasma troponin concentration and odds of death or recurrent myocardial infarction



Bias, confounding, and other reasons for caution

While we excluded patients with clear non-cardiac causes of chest pain, it remains possible that myocardial ischaemia in some patients will be secondary to non-cardiac illness. We also do not yet know whether diagnosing and treating these patients for acute myocardial infarction will improve their clinical outcomes. The true impact of lowering the diagnostic threshold to the 99th centile will be determined only through a prospective controlled trial.

Generalisability to other populations

Our study population comprised consecutive unselected patients with suspected cardiac chest pain rather than a homogeneous group of patients with a clinical diagnosis of acute coronary syndrome receiving optimal treatment. These findings are therefore generalisable to the broad group of patients presenting with chest pain to most acute secondary and tertiary care centres.

Study funding/potential competing interests

The British Heart Foundation support NLM, KAAF, and DEN through an intermediate clinical research fellowship (FS/10/024/28266) and chair awards (CH/92010 and CH/09/002), respectively. NLM and SW have specified relationships with Abbott Diagnostics that might have an interest in the submitted work in the previous three years.

Association between low functional health literacy and mortality in older adults: longitudinal cohort study

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EDITORIAL by Raynor

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STUDY QUESTION

Is health literacy associated with mortality in older adults in England?

SUMMARY ANSWER

A third of older adults had difficulties reading and understanding basic health related written information. Adults with low health literacy, with scores in the lowest 12.5%, were more than twice as likely to die within five years as adults with good understanding of health. Differences in age, wealth, education, baseline health, and health behaviours explained less than half of the increased risk.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Low health literacy is associated with a wide range of adverse health outcomes. One in three adults over the age of 65 in England had difficulty understanding basic health related written information, and this was associated with a higher risk of death over five years, even after accounting for socioeconomic circumstances and baseline health.

Participants and setting

Adults aged 52 or more who participated in the second wave (2004-5) of the English Longitudinal Study of Ageing and survived more than 12 months after interview. Sampling was based on a stratified random sample of households throughout England.

Design, size, and duration

This was a prospective cohort study of 7857 adults followed up over an average of 5.3 years. Participants completed a brief four item test of functional health literacy administered by an interviewer, which assessed understanding of written instructions for taking an aspirin tablet. We obtained data on all cause mortality data from the National Health Service central data registry through October 2009. Mortality risks were estimated by multivariable Cox proportional hazards regression, based on survival time in months.

Main results and the role of chance

Health literacy scores were categorised as high (67.2%), medium (20.3%), or low (12.5%). Low health literacy was associated with older age, poorer baseline health, and indicators of lower socioeconomic position. Overall, 621 deaths occurred during follow-up: 321 (6.1%) in the high health literacy category, 143 (9.0%) in the medium category, and 157 (16.0%) in the low category. After adjusting for age, sex, socioeconomic position, and baseline health, the hazard ratios for all cause mortality were 1.47 (95% confidence interval 1.20 to 1.79) for low health literacy and 1.16 (0.95 to 1.42) for medium health literacy, compared with participants with high health literacy. The hazard ratio for low health literacy remained significant after adjustment for smoking, exercise, and alcohol consumption.

Bias, confounding, and other reasons for caution

The estimate of low health literacy may be an underestimate because adults with low reading ability are less likely to respond to surveys. Overall, 81.5% of eligible participants were interviewed at wave 2 and 94.7% of these completed the assessment for health literacy. Multiple imputation for missing data made no difference to the mortality association.

Generalisability to other populations

Similar findings have been reported within elderly populations in the United States, suggesting that older adults with low health literacy in other developed nations may have a greater risk of mortality. It is not clear whether an association between health literacy and mortality exists for younger adults.

Study funding/potential competing interests

The US National Institute of Aging and a consortium of UK government departments coordinated by the Office for National Statistics funded the English Longitudinal Study of Ageing. SB is supported by a PhD studentship from the British Heart Foundation. AS holds the British Heart Foundation chair of psychology.

Association between health literacy score and all cause mortality

	Hazard ratios (95% CI)*			
Variables	Medium health literacy	P value	Low health literacy	P value
Crude hazard ratio	1.49 (1.23 to 1.82)	<0.001	2.77 (2.29 to 3.35)	<0.001
Adjusted for age and sex	1.24 (1.02 to 1.51)	0.034	1.75 (1.44 to 2.12)	<0.001
As above+socioeconomic position and baseline health	1.16 (0.95 to 1.42)	0.144	1.47 (1.20 to 1.79)	<0.001
As above+health behaviours	1.15 (0.94 to 1.41)	0.168	1.41 (1.15 to 1.73)	0.001

*High health literacy category as reference group.

Credibility of claims of subgroup effects in randomised controlled trials: systematic review

SATIRE Investigators Group

EDITORIAL by Oxman

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STUDY QUESTION

To what extent are authors' claims of subgroup effects in reports of randomised controlled trials credible?

SUMMARY ANSWER

The credibility of claimed subgroup effects, even when claims are strong, is usually low.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous studies have shown that researchers often report subgroup analyses and claim differences in treatment effects among patient subgroups. We assessed the strength of these claims using 10 predefined criteria. Users of this information should treat claims that fail to meet most credibility criteria with a high degree of scepticism.

Proportion of claims meeting subgroup criteria for primary outcome

Criteria	Total (%) (n=64)
Subgroup variable as baseline characteristic	60 (94)
Subgroup variable used as stratification factor at randomisation	13 (20)
Subgroup hypothesis prespecified	26 (41)
Small number (≤5) of subgroup hypotheses tested	28 (44)
Significant interaction test (P<0.05)	6 (9)
Independence of interaction*	1 (5)*
Direction of subgroup effect correctly prespecified	4 (6)
Subgroup effect consistent across studies	21 (33)
Subgroup effect consistent across related outcomes	19 (30)
Compelling indirect evidence	14 (22)

*19 trials had two or more claims.

Selection criteria for studies

We searched Medline for randomised controlled trials published in 2007 in core clinical journals defined by the National Library of Medicine. Teams of two reviewers independently judged whether authors claimed subgroup effects and the strength of their claims, and assessed each of these claims against 10 predefined criteria.

Primary outcome

Credibility of subgroup claims.

Main results and role of chance

207 of 469 randomised controlled trials included in the review reported subgroup analyses, of which 64 made claims for the primary outcome. Of those 64 claims, 20 were strong and 28 of a likely effect. Authors used subgroup variables measured at baseline in 60 (94%) trials. All nine other credibility criteria were satisfied less than 50% of the time, irrespective of strength of claim. In the 19 trials making more than one claim, only one (5%) checked the independence of the interaction. Of the 64 claims, 54 (84%) met four or fewer of the 10 criteria and only five (8%) clearly prespecified the subgroup hypotheses and clearly presented a statistically significant interaction test (P<0.05). A gradient existed in the number of criteria met by the three categories of subgroup claims: strong claim (median 3, interquartile range 2-4), claim for a likely effect (3, 2-3), and suggestion of possible effect (2, 2-3, trend test P=0.016).

Bias, confounding, and other reasons for caution

Our study did not cover all medical journals, and the findings may not be generalisable to all journals. Our study reflects trial reports; the authors may not fully report the information about the conduct and results of subgroup analyses, and contextual evidence. Although we selected the 10 subgroup criteria based on an extensive literature search, and achieved consensus through group discussions, compelling empirical support for these criteria is not available.

Study funding/potential competing interests

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